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Renal function-based versus standard dosing of pemetrexed: a randomized controlled trial

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Abstract

Purpose Pemetrexed is a chemotherapeutic drug in the treatment of non-small cell lung cancer and mesothelioma. Optimized dosing of pemetrexed based on renal function instead of body surface area (BSA) is hypothesized to reduce pharmacokinetic variability in systemic exposure and could therefore improve treatment outcomes. The aim of this study is to compare optimized dosing to standard BSA-based dosing.

Methods A multicenter randomized (1:1) controlled trial was performed to assess superiority of optimized dosing versus BSA-based dosing in patients who were eligible for pemetrexed-based chemotherapy. The individual exposure to pemetrexed in terms of area under the concentration–time curve (AUC) was determined. The fraction of patients attaining to a predefined typical target AUC ($164 \text{ mg} \times \text{h/L} \pm 25\%$) was calculated.

Results A total of 81 patients were included. Target attainment was not statistically significant different between both arms (89% vs. 84% ($p = 0.505$)). The AUC of pemetrexed was similar between the optimized dosing arm ($n = 37$) and the standard of care arm ($n = 44$) ($155 \text{ mg} \times \text{h/L}$ vs $160 \text{ mg} \times \text{h/L}$ ($p = 0.436$)).

Conclusion We could not show superiority of optimized dosing of pemetrexed in patients with an adequate renal function does not show added value on the attainment of a pharmacokinetic endpoint, safety, nor QoL compared to standard of care dosing.

Clinical trial number Clinicaltrials.gov identifier: NCT03655821

Keywords Non-small cell lung cancer · Pemetrexed · Precision dosing · Estimated glomerular filtration rate · Pharmacokinetics

Introduction

The multi-targeted antifolate pemetrexed is a cytostatic agent and frequently used in the treatment of non-small cell lung cancer (NSCLC), mesothelioma and thymoma. Pemetrexed is administered in a dosing regimen of 500 mg/m^2 intravenously every three weeks (Q3W), either alone or in combination with a platinum agent and/or pembrolizumab

[1–3]. Pemetrexed is a hydrophilic drug, and approximately 81% bound to plasma proteins. The kidneys mainly facilitate the elimination of pemetrexed; within 24 h 70–90% of the drug is excreted (both as passive filtration and active secretion) in urine as the unchanged drug [4]. Moreover, it was found that renal function has a pivotal contribution to the total clearance and thus systemic exposure (in terms of the area under the concentration–time curve (AUC) [5, 6]. Both the efficacy and toxicity of treatment with pemetrexed have been related to the systemic exposure [4, 6, 7]. As the risk of severe hematological toxicities increases with renal impairment, treatment with pemetrexed is contra-indicated in patients with a creatinine clearance $< 45 \text{ mL/min}$ [4, 6]. Since the conventional body surface area (BSA)-based dosing does not take into account renal function, patients are

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potentially at increased risk for toxic or sub-therapeutic exposure when applied at the same dose over the full range of creatinine clearances of > 45 mL/min. In the approved dose of 500 mg/m², unwanted high systemic exposure due to pharmacokinetic variability has been linked to an increase in hematological toxicities [7]. Furthermore, it has been proven that impaired renal function is a risk factor for pemetrexed-induced pancytopenia [8]. In terms of efficacy, it was shown that administration of pemetrexed in patients with creatinine clearance > 60 mL/min resulted in poorer efficacy outcomes than in patients with creatinine clearance between 45 and 60 mL/min [9]. To overcome this high variability in exposure to pemetrexed, a dosing strategy based on renal function has been proposed repeatedly [6, 10]. Using a simulation, Latz et al. hypothesized that with a renal function-based dosing strategy, $> 90\%$ of patients would reach a desired target AUC of 164 mg \times h/L $\pm 25\%$, while BSA-based dosing would result in $< 75\%$ attainment. Moreover, Visser et al. showed that dosing based on renal function results in less variability in exposure and thus possibly less expected toxicity [10]. Thus far, this strategy has never been evaluated in a randomized clinical trial. Therefore, the aim of this study was to prospectively investigate dosing of pemetrexed based on renal function.

Materials and methods

Study design and patients

The IMPROVE-II study was a multicenter, open label, randomized (1:1) phase II trial designed to compare optimized renal function-based dosing versus standard of care (BSA-based) dosing of pemetrexed on therapeutic pharmacokinetic target attainment.

The study was approved by the medical ethics committee (Commissie Mensgebonden Onderzoek Regio Arnhem Nijmegen, Nijmegen, The Netherlands, (file number: 2018-4442, Clinicaltrials.gov identifier: NCT03655821)) and written informed consent was obtained for all study participants. All patients with an indication for pemetrexed-based treatment and a predicted creatinine clearance > 45 mL/min (as assessed with the Cockcroft–Gault equation [11]) were eligible to participate in the study. Exclusion criteria were: creatinine-influencing factors (such as obesity (defined as a body mass index (BMI) > 40 kg/m², limb amputation or use of cimetidine or trimethoprim) and hemostatic problems complicating blood sampling procedures. At baseline, the following patient demographics and characteristics were

collected: age, sex, ethnicity (to calculate estimated glomerular filtration rate (eGFR)), weight, height, treatment indication, disease stage, combination therapy, and serum creatinine. The total study period was 12 weeks or four treatment cycles.

Study objectives and endpoints

The primary objective of this study was to assess whether the optimized dosing of pemetrexed in patients based on renal function led to a higher proportion of patients attaining to a pharmacokinetic target than when patients were dosed on BSA. For exploratory purposes, we performed a post hoc subgroup analysis, dividing the patients in each treatment group into two groups based on the median value of creatinine clearance in the study population.

Secondary objectives included the incidence of hematological adverse events, the incidence of toxicity-related dose reductions, treatment delays (defined as > 3 days delay) and treatment discontinuation, and the patients' quality of life during study participation.

Justification of the pharmacokinetic target

A pharmacokinetic target was chosen based on several considerations. First, pemetrexed can be administered in different treatment modalities. Besides monotherapy, doublet or triple therapy with platinum agents and/or programmed death protein 1 (PD-1) immunotherapy are all applied. This not only leads to a wide variety of possible treatment schedules, but possibly also to a partial overlap in efficacy and toxicity, complicating the identification of individual effects of pemetrexed. Secondly, the patient group receiving pemetrexed is heterogeneous. Treatment indication, disease stage and treatment line are all highly variable within the treated population. As large numbers of patients would be required, a study based on response measures was not considered feasible. Since pemetrexed exposure has been shown to be a good predictor for efficacy and safety [7], a pharmacokinetic endpoint is the most sensitive and unbiased endpoint for a dose individualization study.

An AUC of 164 mg \times h/L was previously shown to be a safe and effective target [7]. In addition, it was shown that a large proportion of patients ($> 90\%$) receiving pemetrexed in a dose based on their estimated renal function would reach within 75–125% of this target, while less than three-quarter

of patients receiving a dose based on BSA would fall within this target AUC range [6, 7].

Safety

The occurrence of grade II and grade III/IV anemia, leukopenia, neutropenia, and thrombocytopenia (Common Terminology Criteria for Adverse Events (CTCAE v5.0)) were investigated.

Quality of life

The incidence of dose delays and dose reductions was assessed, as these relate directly to toxicity. Moreover, two validated quality of life questionnaires (the general EORTC QLQ-C30 and the lung cancer-specific EORTC LC13) were taken and scored at baseline and 12 weeks after study treatment initiation [12].

Treatment

In line with the product label, pemetrexed and concomitant chemo-and/or immunotherapy were administered intravenously in a 21-day treatment cycle. The infusion duration of pemetrexed was approximately ten minutes. Patients in the standard of care arm received pemetrexed in the approved dose of 500 mg/m². The optimized renal function-based dose was derived from the previously established and validated relationship between creatinine clearance (assessed with the Cockcroft–Gault equation) and pemetrexed clearance [13]. Since, dose = AUC × clearance, the dose was calculated with the following equation:

$$\text{Dose (mg)} = 423 + 464 \\ \times (\text{creatinine clearance (mL/min)} / 92.6).$$

Every cycle, the optimized dose was recalculated based on the most recent creatinine clearance. Concomitant (chemo)-immunotherapy and co-medications were administered following standard local treatment protocols.

Randomization

Patients were randomly assigned to either the optimized dosing arm or standard of care arm in a 1:1 ratio using

an automated system with variable block randomization (block sizes: 4, 6, 8) (Castor EDC v.14.81).

Pharmacokinetic sampling and bioanalysis

One pharmacokinetic curve was obtained for each patient, and individual exposure was determined using a previously validated limited sampling schedule (four samples taken at 0.5–1, 1–2, 4–5 and 6–8 h after the start of pemetrexed infusion, allowing for a complete and accurate estimation of the AUC) [14]. Samples were analyzed using a validated assay using ultra-high-performance liquid chromatography coupled with an ultraviolet detector, as published previously [15].

Statistical analysis

Based on Monte Carlo simulations on a validated pharmacokinetic model [13], we expected that approximately 60% of the patients would reach therapeutic exposure when pemetrexed was dosed on BSA compared to 85% of the patients when pemetrexed was dosed based on renal function. To show the superiority of renal function-based dosing compared to standard of care dosing, assuming an improvement of attainment of therapeutic exposure from 60 to 85%, a total of 94 patients (47 per treatment arm) were needed to be included to reach a power of 80% with a significance level of 5% (two-sided). Due to the halted accrual of patients during the COVID-19 pandemic, an unplanned interim analysis was performed in April 2021 after the inclusion of 81 out of 94 patients. Worst- and best-case scenarios for the primary outcome were tested to justify pre-term analysis. The best-case scenario was defined as the scenario in which all future patients randomized in the optimized dosing arm would attain the target AUC, while all patients in the standard-of-care-dosing arm would fall outside this target. Conversely, the worst-case scenario would represent all upcoming patients in the standard-of-care-dosed arm to reach target AUC, while optimized dosing would not yield in target attainment.

The individual pemetrexed clearance was calculated based on the obtained pharmacokinetic data by means of Bayesian estimation. A post hoc analysis of the pharmacokinetic data on a previously validated pharmacokinetic model was performed in NONMEM (version 7.4, Icon, Ireland). Subsequently, the individual AUC was calculated by dividing the administered pemetrexed dose by the individual calculated clearance.

Table 1 Baseline characteristics and primary outcome measures for the BSA group, renal function group and the total patient group

	BSA (<i>n</i> = 44)	Renal function (<i>n</i> = 37)	Total (<i>n</i> = 81)
Diagnosis <i>n</i> (%)			
NSCLC	35 (80%)	27 (73%)	62 (77%)
Mesothelioma	7 (16%)	9 (24%)	16 (20%)
Thymoma	2 (5%)	1 (3%)	3 (4%)
First-line treatment <i>n</i> (%)	25 (57%)	21 (54%)	46 (56%)
Age	63 (57–69)	67 (59–72)	65 (58–71)
Gender (<i>n</i> of male (%))	16 (36%)	22 (59%)	38 (47%)
BSA (m ²)	1.87 (1.71–2.00)	1.95 (1.78–2.00)	1.91 (1.75–2.00)
estimated creatinine clearance (mL/min)	99.3 (84.0–118.4)	93.8 (78.7–101.4)	95.2 (83.6–111.7)
CKD-EPI (mL/min/1.73 m ²)	94.6 (81.9–100.5)	85.1 (80.1–93.5)	90.1 (80.9–98.9)
Treatment cycles	4 (4–4)	4 (4–4)	4 (4–4)
Pemetrexed dose (mg) per cycle	950 (850–1000)	850 (818–885)	885 (825–975)
Concomitant oncological therapy			
None	8 (18%)	7 (19%)	15 (19%)
Carboplatin	11 (25%)	12 (32%)	23 (28%)
Carboplatin + pembrolizumab	18 (41%)	11 (30%)	29 (36%)
Cisplatin	4 (9%)	5 (14%)	9 (11%)
Cisplatin + pembrolizumab	3 (7%)	2 (5%)	7 (9%)

Characteristics are presented as median with interquartile range unless otherwise specified

BSA body surface area, NSCLC non-small cell lung cancer

A subgroup analysis was performed based on a creatinine clearance < 95 mL/min and ≥ 95 mL/min. Due to the limited range in renal function in the study population, the median was chosen as a cut-off value instead of standard cut-offs (i.e., 90–60–30 mL/min), to facilitate a balanced distribution in the number of subjects in both groups.

As pharmacokinetic parameters often follow a log-normal distribution, AUCs per group are presented as geometric mean. A Chi-squared test was performed to test for statistically significant difference (*p* value < 0.05) in the fraction of patients attaining to target between both treatment arms. Regarding the subgroup analysis, statistically significant differences (*p* value < 0.05) in AUC were assessed using a Mann–Whitney *U* test. A Chi-square test was performed to test for statistically significant difference (*p* value < 0.05) in the fraction of patients that experienced ≥ 1 hematological toxicity event between groups. Each subcategory of the quality-of-life questionnaire resulted in a score between 0 and 100 per patient. Median scores are presented as median (+ range). Change in quality of life was calculated (end of study versus baseline). Results of patients who were not able to complete both questionnaires were excluded from the dataset. Statistically significant differences (*p* value < 0.05)

between the two treatment groups were calculated using a Mann–Whitney *U* test.

All statistical analyses were performed using the R software package V4.1.0 [16].

Results

Patient characteristics and pharmacokinetic analysis

Between March 2019 and April 2021, a total of 81 patients were included in the study, 44 in the standard-of-care arm and 37 in the optimized dosing arm. The difference in group size was mostly due to a combination of the block randomization and dropout shortly after randomization (before start of cycle treatment 1, due to the vulnerability of the study population). Moreover, one patient was accidentally treated with a BSA-based dose while randomized in the optimized dosing arm, consequently this patient was further evaluated as per given treatment. The baseline characteristics were comparable between groups (Table 1). The majority of patients were diagnosed with NSCLC and received pemetrexed as a part of the first-line treatment. Presented

in Table 2 is the target attainment for both groups. The geometric mean AUCs were 159.9 and 154.7 mg × h/L for the BSA and the optimized dosing group, respectively. Target attainment was not statistically significant different between both groups ($p = 0.505$).

The median creatinine clearance in the study population was 95 mL/min, therefore, the subgroup analysis was based on a creatinine clearance < 95 mL/min and ≥ 95 mL/min. Figure 1 visualizes the AUC of pemetrexed in both randomization groups when subdivided. As expected, when only looking at the standard of care arm, a statistically significant difference in pemetrexed AUC was observed between the creatinine clearance subgroups ($p = 0.003$). This confirms that with decreasing renal function, exposure increases when dosed on BSA. This was not observed for the optimized dosing arm ($p = 0.34$). Overall, a higher percentage of patients in the optimized dosing arm attained to the target AUC (37 out of 44 patients) when compared to patient in the standard-of-care dosing arm based on the creatinine clearance group (33 out of 37 patients), albeit not statistically significant. Figure 1 clearly visualizes that for patients with creatinine clearance < 95 mL/min dosed on BSA, a higher median AUC

Table 2 Target attainment (based on total and subgroups of the population) and geometric mean AUC for the BSA group and the renal function group in total and in the subgroup analysis

	BSA ($n = 44$)	Renal function ($n = 37$)	p value
AUC (mg × h/L)			
Total	159.9 (145.0–176.0)	154.7 (137.6–171.5)	0.436
≥ 95 mL/min	154.2 (141.5–163.9)	151.0 (136.8–160.1)	0.908
< 95 mL/min	176.3 (156.0–196.7)	163.3 (143.6–172.3)	0.073
Target attainment n (%)			
Total	37 (84.1)	33 (89.1)	0.505
≥ 95 mL/min	23 (88.5%)	15 (93.8%)	0.571
< 95 mL/min	14 (77.8%)	18 (85.7%)	0.520

AUCs are presented median with interquartile range. Target attainment was defined as reaching an individual AUC of 123–205 mg × h/L

and greater variability in exposure were observed compared to patients receiving optimized dose ($p = 0.07$). This trend was not observed for patients with creatinine clearance ≥ 95 mL/min.

To justify the pre-term analysis of 81 patients, we calculated the outcomes of a best-case and worst-case scenario. In case of both scenarios (all remaining patients in the individualized group ($n = 10$) on target and all

remaining patients in the BSA group off target ($n = 3$) or vice versa), no significant difference was observed ($p = 0.082$ and $p = 0.083$).

Safety

Table 3 shows the number of patients that experienced ≥ 1 hematological toxicity event. One patient in the optimized dosing arm was excluded from this analysis due to incorrect (BSA-based) dosing from cycle 2 onward. Overall, there were no statistically significant differences between groups. Grade II anemia occurred in approximately 40–50% of patients. The incidences of grade III/IV hematological events were relatively low, ranging from 0 to 15.9%. Treatment delays and dose reductions due to toxicity occurred equally in both groups. Reported reasons other than hematological toxicity included hypokalemia, diarrhea, vomiting, kidney injury, pericarditis, fatigue, pneumonia, diverticulitis, and auto-immune reaction.

Quality of life

In total, 58 patients completed the QLQ-C13 questionnaire both at baseline and after 12 weeks of pemetrexed therapy. The lung cancer-specific LC13 questionnaire was filled in by 54 patients. Within-patient baseline and end of treatment scores were not statistically significant different in any of the four categories as indicated by the EORTC (functional scale, quality of life, symptom scale and the specific lung cancer scale). A wide range in change between $t = 12$ weeks and baseline questionnaire was observed with the median around zero in both groups. Median changes and ranges are presented in Table 4. The change in end of treatment versus baseline score was not statistically significant different between groups.

Discussion

In the era of precision medicine, one should also aim to implement precision dosing. In this study, we hypothesized that patients would benefit from optimized dosing of pemetrexed. We found that an optimized renal function-based pemetrexed dosing did not result in higher pharmacokinetic target attainment compared to standard of care BSA dosing.

Fig. 1 Boxplots for the AUC per subgroup. The box represents the 25th–75th percentiles with geometric mean, the whiskers indicate the 2.5th–97.5th percentile and the dots visualize the outlying observation. The target AUC ± its 25% range are depicted by the horizontal dashed lines. *BSA* body surface area, *RF* renal function

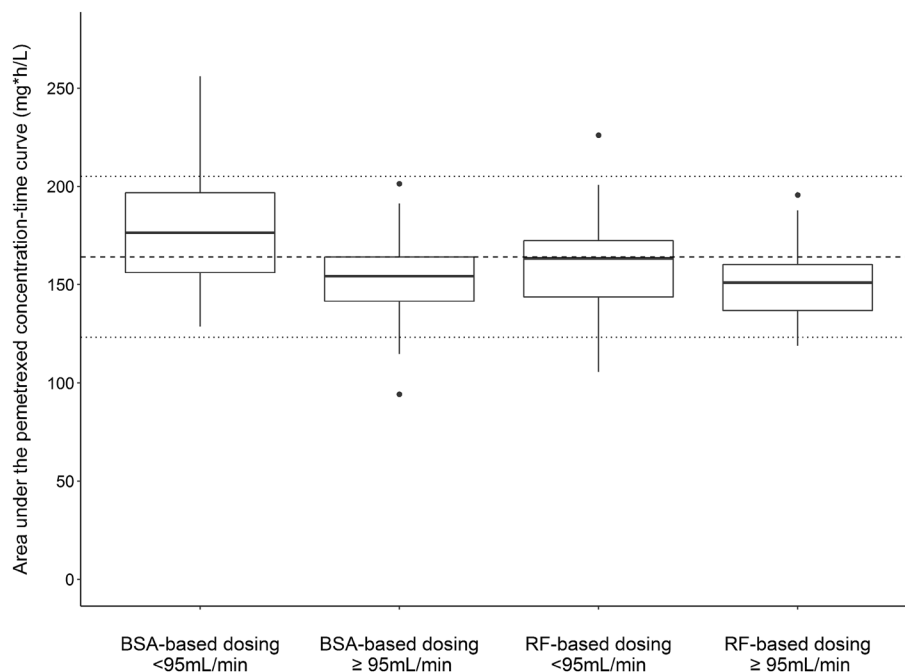


Table 3 Fraction of patients experiencing at least (≥ 1) toxicity event in both groups

	BSA-based (n=44)	Renal function-based (n=36)	p value
Anemia			
Grade 2	22 (50.0%)	14 (38.9%)	0.32
≥Grade 3	1 (2.2%)	4 (11.1%)	0.10
Leukopenia			
Grade 2	3 (6.8%)	2 (5.5%)	0.82
≥Grade 3	0	0	–
Neutropenia			
Grade 2	15 (34.1%)	9 (25.0%)	0.38
≥Grade 3	7 (15.9%)	4 (11.1%)	0.54
Thrombopenia			
Grade 2	3 (6.8%)	0	–
≥Grade 3	1 (2.2%)	1 (2.8%)	0.89
Cycle delay	13 (29.5%)	9 (25.0%)	0.65
Dose reductions	5 (11.4%)	3 (8.3%)	0.65

Results are presented as n (%)

Table 4 The difference in end of treatment versus baseline score per subgroup of the EORTC-C13 and LC13 questionnaires

	BSA-based (n=33)	Renal function-based (n=25)	p value
Functional scale	– 2.2 (– 44 to +44)	– 2.2 (– 27 to +33)	1.0
Quality of life	0 (– 50 to +67)	– 8.8 (– 58 to +50)	0.37
Symptom scale	0 (– 39 to +47)	– 1.4 (– 17 to +22)	0.55
Specific lung cancer scale	– 1.4 (– 44 to +22)	– 2.8 (– 19 to +19)	0.82

Scores are presented as median (range)

Moreover, no significant differences were observed with regards to safety events and quality of life. With this randomized study, we were the first to prospectively evaluate a renal function dosing regimen of pemtrexed.

The target attainment in the optimized dosing group (89.1%) was as expected, while in the BSA-based dosing group, the target attainment (84.1%) was much higher than expected. This is possibly due to the limited number of patients in the extremes of the renal function range (creatinine clearance 45–60 or > 125 mL/min), thus resulting in a limited variation in exposure. This could also explain why we did not find a statistically significant difference in target attainment between both groups and only a small variation in administered dose within the optimized dosing arm. In retrospect, as limited variability in renal function was observed, questions might rise regarding the power of this study. Therefore, it is difficult to draw definitive conclusions. Interestingly, there was a significant difference in AUC in the subgroup analysis within the BSA-based dosing group when stratified on renal function (p=0.003). This confirms the strong influence of renal function on exposure if not

taken into account with dosing. Especially in patients with a mild renal impairment (creatinine clearance: 45–60 mL/min), dosing based on renal function could serve a pivotal role in attaining a target systemic exposure. This is reflected in the observed exposure within the standard dosing group. Patients with a creatinine clearance < 95 mL/min show higher exposure and greater variability compared to patients with a creatinine clearance \geq 95 mL/min ($p=0.07$). Although this finding was not statistically significant, this trend indicates that patients with decreased renal function could benefit from this strategy due to a decrease in pharmacokinetic variability. The limited number of patients in the extremes of the renal function range also reflects in the low variation in the administered pemetrexed dose in the optimized dosing group. Moreover, the median administered pemetrexed dose is lower in the optimized dosing group (850 mg) compared to the BSA-based group (950 mg). The median dose in the optimized dosing group corresponds with the calculated doses based on creatinine clearance. Although the median dose is lower, target exposure is attained ($164 \text{ mg} \times \text{h/L} \pm 25\%$) and efficacy is thus not compromised.

The large population pharmacokinetic analysis by Latz et al. was used as a premise for the individualized dosing strategy in this clinical study. In their analysis, they present creatinine clearance as a covariate for systemic pemetrexed clearance [13]. Nowadays, creatinine clearance is being widely substituted by the estimated glomerular filtration rate (calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation), as this gives a more accurate prediction of renal function [17]. We recently studied the investigation of several renal function markers for prediction of pemetrexed clearance. In this analysis, creatinine clearance based on the Cockcroft–Gault was confirmed as an appropriate predictor of pemetrexed clearance, yet we found that using the CKD-EPI resulted in a slightly (statistically significant, clinically irrelevant) improved prediction: the unexplained variability in clearance reduced from 23.3 to 21% with CKD-EPI versus Cockcroft–Gault [5]. Thus, we expect this would not affect the non-significant outcome difference in this analysis in patients with adequate renal function. This is supported by the results of a simulation study on the pharmaco-economic benefits of renal function-based dosing of pemetrexed. The AUC range obtained in the subjects with pemetrexed dose based on CKD-EPI is similar to that reported in this study (AUC (median [IQR]) $158 [136\text{--}183] \text{ mg} \times \text{h/L}$ versus $154.7 [137.6\text{--}171.5] \text{ mg} \times \text{h/L}$) [18]. Cachexia is often observed in patients with lung

cancer [19, 20], resulting in seemingly low serum creatinine concentrations and thus overestimation of renal function. When deploying a renal function-based dosing strategy, this could theoretically lead to overdosing and thus increased exposure and higher risk for toxicity.

The primary pharmacokinetic driver for pemetrexed efficacy has not been extensively studied. Thus, targeting the AUC of pemetrexed to maintain efficacy is debatable. In the early phase I studies of pemetrexed, several dosing regimens were investigated which might offer some clues regarding the exposure–response relationship of this drug. The maximum tolerated doses for daily and weekly schedules were found to be only 4 mg/m^2 and 40 mg/m^2 , leading to hematological toxicity without efficacy. On the contrary, 3-weekly dosing of 600 mg/m^2 was shown to be an effective strategy [21–23]. This indicates that efficacy and toxicity of pemetrexed are driven by different pharmacokinetic parameters. For methotrexate, another folate antimetabolite, it has been found that anti-tumor efficacy in lymphoma is driven by its AUC, while toxicity was related to the time-above-threshold concentration. Recently, we found that the hematological toxicity of pemetrexed, in particular neutropenia, is also more likely to be time-above-threshold-driven instead of total exposure [24]. In an earlier study, an effective target AUC of $164 \text{ mg} \times \text{h/L}$ for pemetrexed was proposed. This could indicate that an AUC-based dosing could optimize the efficacy of therapy, while the threshold concentrations during therapy should be monitored to prevent major toxicities. However, this is particularly relevant in patients with renal impairment. In patients with adequate renal function, AUC and time-above-threshold are closely related, in contrast to patients with renal impairment [24]. Our results indeed show no statistical significant differences in hematological toxicities between both dosing arms, underlining this hypothesis.

In our study, pemetrexed was often administered in a doublet- or triple-drug regimen, concomitantly with a platinum-based cytostatic agent (and pembrolizumab). Since there is an overlap in toxicity profiles of these drugs, the sole toxicological effect of pemetrexed could not be established. However, concomitant administration is standard care for the treatment of NSCLC, the observed incidences of toxicities might be more representable for the clinical practice.

For methotrexate, limited data are available regarding the effect of renal function on its pharmacokinetics. In adults, only one retrospective study has evaluated this effect and observed a negative correlation between the methotrexate plasma concentration and the estimated renal function [25].

This would rationalize the investigation of renal function-based dosing for this drug. However, methotrexate within oncology is given at doses that could be lethal without supportive measures (such as hydration and administration of folic acid), obviating the need for optimized dosing based on renal function to overcome toxicity.

From a patient's perspective, quality of life is a valuable study endpoint. It is rather difficult to assess quality of life in relatively small patient groups ($n=44$ and 37 , respectively in our study). For pemetrexed as a single agent, two studies reported that quality of life during pemetrexed maintenance therapy was similar to placebo [26, 27]. The scores at baseline and 12 weeks are comparable to our findings. Quality of life can be negatively influenced by factors such as progression of disease (non-responders) or severe treatment toxicity. However, in case of partial or complete response to treatment without toxicity, quality of life can improve. Moreover, our relatively small patient groups are heterogeneous in terms of diagnosis, disease stage, treatment modality and treatment line. This is reflected in the wide range in differences between baseline and end of treatment for both groups we observed.

In conclusion, with the results of our study, we could not support the superiority of renal function-based dosing of pemetrexed in patients with adequate renal function. Further research in patients with moderate renal function is needed to explore possible benefits in this specific patient group.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest Nikki de Rouw, Rene Boosman, Sjaak Burgers, Alwin Huijtema, Hieronymus Derijks, David Burger, Bonne Biesma, Melinda Pruis Sander Croes, Michel van den Heuvel and Rob ter Heine declare that they have no conflicts of interest that might be relevant to the contents of this manuscript. Anne-Marie Dingemans: received financial support from advisory boards Sanofi, Amgen, Bayer, Eli-Lilly and Roche and as lecturer from Jansen, Pfizer and AstraZeneca. Outside the submitted work. Berber Piet: is/was a member of the advisory boards of Takeda, Bristol Meyer Squibb and received lecturer fees from Astra Zeneca and Pfizer, outside the submitted work. Lizza Hendriks: received re-search funding from Roche, Boehringer-Ingelheim, AstraZeneca and Takeda (all to the institution); is/was a member of the advisory boards for Boehringer-Ingelheim, BMS, Eli-Lilly, Roche, Pfizer, Takeda, MSD and Amgen (all institutional, except once for Roche); received travel and conference reimbursements from Roche; provided funded mentorship sessions with key opinion leaders from AstraZeneca, received fees for webinars/medtalks from AstraZeneca and funded interview sessions from Roche (to the institution); is a local principal investigator in clinical trials from AstraZeneca, Novartis, BMS, MSD, Merck, GSK, Takeda, Blueprint, Roche, Janssen Pharmaceuticals and Miroti. All outside the submitted manuscript. Daphne Dumoulin: received payment for presentations of MSD, Roche, Astra Zeneca, Novartis, BMS. Received support for attending a congress paid by Novartis, outside the submitted work. Ron Mathijssen: received grants from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Pamgene, Pfizer, Novartis, Servier and Roche, personal fees from Novartis and Servier and holds a patent from Pamgene, outside the submitted work.

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Consent to participate Written informed consent was obtained for all study participants.

Consent for publications Not applicable.

References

- Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al (2018) Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 29(Suppl 4):192–237. <https://doi.org/10.1093/annonc/mdy275>
- Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S et al (2015) Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26(Suppl 5):v31–v39. <https://doi.org/10.1093/annonc/mdv199>
- Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S, Committee EG (2015) Thymic epithelial tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26(Suppl 5):v40–55. <https://doi.org/10.1093/annonc/mdv277>
- European Medicine Agency (EMA). ALIMTA EPAR - Product Information. 2017. Available via: <https://www.ema.europa.eu>
- de Rouw N, Boosman RJ, Huitema ADR, Hilbrands LB, Svensson EM, Derijks HJ et al (2021) Rethinking the application of pemetrexed for patients with renal impairment: a pharmacokinetic analysis. *Clin Pharmacokinet*. <https://doi.org/10.1007/s40262-020-00972-1>
- Mita AC, Sweeney CJ, Baker SD, Goetz A, Hammond LA, Patnaik A et al (2006) Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *J Clin Oncol* 24(4):552–562. <https://doi.org/10.1200/JCO.2004.00.9720>
- Latz JE, Rusthoven JJ, Karlsson MO, Ghosh A, Johnson RD (2006) Clinical application of a semimechanistic-physiologic population PK/PD model for neutropenia following pemetrexed therapy. *Cancer Chemother Pharmacol* 57(4):427–435. <https://doi.org/10.1007/s00280-005-0035-2>
- Ando Y, Hayashi T, Ujita M, Murai S, Ohta H, Ito K et al (2016) Effect of renal function on pemetrexed-induced haematotoxicity. *Cancer Chemother Pharmacol* 78(1):183–189. <https://doi.org/10.1007/s00280-016-3078-7>
- Chen CY, Lin JW, Huang JW, Chen KY, Shih JY, Yu CJ et al (2015) Estimated creatinine clearance rate is associated with the treatment effectiveness and toxicity of pemetrexed as continuation maintenance therapy for advanced nonsquamous non-small-cell lung cancer. *Clin Lung Cancer* 16(6):e131–e140. <https://doi.org/10.1016/j.clcc.2015.01.001>
- Visser S, Koolen SLW, de Bruijn P, Belderbos HNA, Cornelissen R, Mathijssen RHJ et al (2019) Pemetrexed exposure predicts toxicity in advanced non-small-cell lung cancer: a prospective cohort study. *Eur J Cancer* 121:64–73. <https://doi.org/10.1016/j.ejca.2019.08.012>
- Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. *Nephron* 16(1):31–41. <https://doi.org/10.1159/000180580>
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al (1993) The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85(5):365–376. <https://doi.org/10.1093/jnci/85.5.365>
- Latz JE, Chaudhary A, Ghosh A, Johnson RD (2006) Population pharmacokinetic analysis of ten phase II clinical trials of pemetrexed in cancer patients. *Cancer Chemother Pharmacol* 57(4):401–411. <https://doi.org/10.1007/s00280-005-0036-1>
- de Rouw N, Visser S, Koolen SLW, Aerts J, van den Heuvel MM, Derijks HJ et al (2020) A limited sampling schedule to estimate individual pharmacokinetics of pemetrexed in patients with varying renal functions. *Cancer Chemother Pharmacol* 85(1):231–235. <https://doi.org/10.1007/s00280-019-04006-x>
- van den Hombergh E, de Rouw N, van den Heuvel M, Croes S, Burger DM, Derijks J et al (2020) Simple and rapid quantification of the multi-enzyme targeting antifolate pemetrexed in human plasma. *Ther Drug Monit* 42(1):146–150. <https://doi.org/10.1097/FTD.0000000000000672>
- R Core Team (2020). R: a language and environment for statistical computing. R foundation for statistical computing, Vienna, Austria. URL <https://www.R-project.org/>
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI et al (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150(9):604–612. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006>
- de Rouw N, de Boer M, Boosman RJ, van den Heuvel MM, Burger DM, Lieverse JE et al (2022) The pharmacoeconomic benefits of pemetrexed dose individualization in patients with lung cancer. *Clin Pharmacol Ther* 111(5):1103–1110. <https://doi.org/10.1002/cpt.2529>
- Kimura M, Naito T, Kenmotsu H, Taira T, Wakuda K, Oyakawa T et al (2015) Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. *Support Care Cancer* 23(6):1699–1708. <https://doi.org/10.1007/s00520-014-2534-3>
- Zhu R, Liu Z, Jiao R, Zhang C, Yu Q, Han S et al (2019) Updates on the pathogenesis of advanced lung cancer-induced cachexia. *Thorac Cancer* 10(1):8–16. <https://doi.org/10.1111/1759-7714.12910>
- Rinaldi DA, Burris HA, Dorr FA, Woodworth JR, Kuhn JG, Eckardt JR et al (1995) Initial phase I evaluation of the novel thymidylate synthase inhibitor, LY231514, using the modified continual reassessment method for dose escalation. *J Clin Oncol* 13(11):2842–2850. <https://doi.org/10.1200/jco.1995.13.11.2842>
- Rinaldi DA, Kuhn JG, Burris HA, Dorr FA, Rodriguez G, Eckhardt SG et al (1999) A phase I evaluation of multitargeted antifolate (MTA, LY231514), administered every 21 days, utilizing the modified continual reassessment method for dose escalation. *Cancer Chemother Pharmacol* 44(5):372–380. <https://doi.org/10.1007/s002800050992>
- McDonald AC, Vasey PA, Adams L, Walling J, Woodworth JR, Abrahams T et al (1998) A phase I and pharmacokinetic study of LY231514, the multitargeted antifolate. *Clin Cancer Res* 4(3):605–610
- Boosman RJ, Dorlo TPC, de Rouw N, Burgers JA, Dingemans AC, van den Heuvel MM et al (2021) Toxicity of pemetrexed during renal impairment explained—implications for safe treatment. *Int J Cancer*. <https://doi.org/10.1002/ijc.33721>
- Yang Y, Wang X, Tian J, Wang Z (2018) Renal function and plasma methotrexate concentrations predict toxicities in adults receiving high-dose methotrexate. *Med Sci Monit* 24:7719–7726. <https://doi.org/10.12659/msm.912999>
- Belani CP, Brodowicz T, Ciuleanu TE, Krzakowski M, Yang SH, Franke F et al (2012) Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study. *Lancet Oncol* 13(3):292–299. [https://doi.org/10.1016/S1470-2045\(11\)70339-4](https://doi.org/10.1016/S1470-2045(11)70339-4)
- Gridelli C, de Marinis F, Pujol JL, Reck M, Ramlau R, Parente B et al (2012) Safety, resource use, and quality of life in paramount: a phase III study of maintenance pemetrexed versus placebo after induction pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol* 7(11):1713–1721. <https://doi.org/10.1097/JTO.0b013e318267cf84>

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